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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,300	08/21/2001	Todd Lewis Talarico	35780/233666 (5780-5)	8297

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/934,300	Applicant(s) TALARICO ET AL.	
	Examiner S. Devi, Ph.D.	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-19 ~~is/are~~ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-19 ~~is/are~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Response to Applicants' Amendment/Response

Applicants' Response

- 1) Acknowledgment is made of Applicants' after-final response filed 02/15/04 in response to the final Office Action mailed 11/16/04.

Finality Withdrawn

- 2) The finality of the previous Office Action mailed 11/16/04 is withdrawn in light of the additional explanation/discussion set forth below, which is necessitated by Applicants' response.

Status of Claims

- 3) No claims have been amended via the after-final amendment filed 02/15/04.
Claims 12-19 are pending and are under examination.

Prior Citation of Title 35 Sections

- 4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

- 5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

- 6) The rejection of claims 14 made in paragraph 10 of the Office Action mailed 11/16/04 under 35 U.S.C. § 103(a) as being unpatentable over Nho *et al.* (US 5,234,903 - Applicants' IDS) as applied to claim 13 above and further in view of Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993, already of record), is withdrawn.

Rejection(s) Maintained

- 7) The rejection of claims 12, 13, 15, 16, 18 and 19 made in paragraph 9 of the Office Action mailed 11/16/04 under 35 U.S.C. § 102(b) as being anticipated by Nho *et al.* (US 5,234,903 - Applicants' IDS), is maintained for reasons set forth therein and herebelow. Claim 14 is added to this rejection since Nho/Davis indeed taught ethanol as a solvent for dissolving activated PEG. See

below.

With regard to the disclosure of Nho *et al.*, Applicants submit the following arguments;

(a) The claimed methods require that the aPEG solution must first be dissolved in an appropriate solvent and then filtered before using the aPEG solution to chemically modify hemoglobin. A critical element of the claimed invention is the use of a filtered aPEG solution to chemically modify hemoglobin. A *prima facie* case of anticipation under 35 U.S.C. § 102 has not been established. Nho *et al.* teach a method for producing a chemically modified hemoglobin solution comprising modifying a hemoglobin solution to remove contaminants (e.g., endotoxin). Nho's method does not teach first dissolving the aPEG in a solvent and then filtering the aPEG solution to substantially reduce contaminant levels prior to combining the aPEG solution with the haemoglobin solution. The reference teaches that the aPEG is added to the haemoglobin fraction in a powdered form.

(b) Synthesis and activation of the aPEG taught by Nho *et al.* requires several intermediate reaction steps as stated in lines 1-39 of column 14. The process involves dissolving the unactivated PEG in a solvent, drying the solution, redissolving the residue in a solvent, activating, filtering and drying again. The resulting residue is dissolved in a solvent, filtered from trace insolubles and collected to facilitate precipitation of the aPEG, which is then collected by filtration followed by recrystallization as a white powder. This powder is reacted with the haemoglobin solution to produce a chemically modified haemoglobin. Nho *et al.* simply do not teach dissolving the aPEG in a solvent, filtering it to substantially reduce contaminant levels, and then combining this filtered aPEG solution with a haemoglobin solution. The steps of dissolving and filtering occur only during the synthesis and activation of the solid aPEG and do not equate with the production of a stabile solution.

(c) Even if Nho *et al.* taught an aPEG solution, the filtration steps performed during synthesis of the aPEG would be insufficient to substantially reduce the level of contaminants, because these steps involve removal of residual chemical reactants and filtration from 'trace insolubles', not the substantial reduction in contaminants required by the present claims. Only after chemical modification is the hemoglobin solution of Nho *et al.* filtered and sterilized to substantially reduce contaminant levels. The reduction in endotoxin levels reported in Table IV is due to

filtration and sterilization of the final haemoglobin product post-chemical modification and is not the result of filtering an aPEG solution prior to combining it with haemoglobin. The haemoglobin solution produced by the claimed methods cannot be purified after chemical modification because such filtration would disrupt, or even destroy, the haemoglobin composition.

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons. Nho's method or steps are not limited to those described in column 14. With regard to the steps of dissolving aPEG in a solvent in which it is stabile and filtering the dissolved aPEG through one filter to obtain a filtered aPEG solution, Nho's method encompasses these steps. For instance, Nho *et al.* taught at lines 19-21 of column 13 that '[a]ny method known in the art may be used to activate the polyalkylene oxide for subsequent conjugation to hemoglobin'. One of the patents cited all through Nho *et al.* is US patent 4,179,337 ('337) issued to Davis *et al.* 'which is incorporated by reference in its entirety' within Nho's patent '337. See section 2.6, the last five lines in particular. At section 2.6, Nho *et al.* specifically disclosed a PEGylation process as detailed in US patent 4,179,337. This '337 patent is also cited by Nho *et al.* at line 34 of column 13. The pertinent parts of the disclosure by Davis *et al.* ('337) are discussed herein to rebut Applicants' arguments. Davis *et al.* ('337) is hereby made of record. A review of Davis *et al.* ('337), which is expressly incorporated by reference within the cited art of Nho *et al.*, establishes the following.

A PEG was activated in a solvent and the resultant solution was filtered. The filtrate precipitated polymer was dissolved in ethanol, i.e., the same solvent recited in the instant claim 14, and the ethanol solution of the activated PEG was used in the PEGylation process (see Example VIII of Davis *et al.*). The Davis' activated PEG solution is expressly encompassed within the disclosure of Nho *et al.* due to Nho's express incorporation by reference. Although Davis *et al.* do not expressly mention the limitation 'stabile' in the identified part of their disclosure, that the activated PEG is stabile in ethanol is inherent from the teachings of Davis *et al.*, because one of the solvents used by Applicants is Davis' ethanol solvent (see instant claim 14). Ethanol inherently and necessarily confers stability to activated PEG. Since the solvent ethanol used both by the prior art and the Applicants is one and the same, it has to necessarily confer the same stability on the activated PEG. Although Davis' disclosure, incorporated by reference within Nho's patent, does not expressly state that Davis' filtering step 'substantially reduces the levels of contaminants' as

recited broadly in instant claim 1, or 'substantially reduces endotoxin contaminant levels' as recited in the instant claim 15, Davis' filtration step is expected to 'substantially reduce' the levels of any generic 'contaminants' or specifically 'endotoxin contaminant levels'. It is well known in the art that such a filtration process does remove contaminants, irrespective of whether they are unreacted reactants or reagents, bacterial contaminants or endotoxin contaminants. Claims 12-14 do not identify 'contaminants' by name and therefore the term broadly includes residual chemical reactants, trace insoluble materials, bacteria, fungi and their products etc. In fact at lines 7 and 8 on page 6, the instant specification defines the term 'contaminants' as referring to compounds that include particulates and bioburden. Davis' filtration step is viewed as yielding substantial reduction in the levels of bacterial or fungal contaminants, reactants, or particulates, or reduction in endotoxin contaminant levels by at least 500 EU/cm² of filter area, absent evidence to the contrary. Since the Office does not have the facilities for examining and comparing the level of reduction of contaminants in Applicants' aPEG and the prior art aPEG, the burden is on the Applicants to show a novel or an unobvious difference between the instant invention and the prior art invention, i.e., to show that the prior art filtering step does not result in the same substantial reduction in the levels of contaminants as instantly recited. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 05 USPQ 594.

Since the disclosure of Davis' patent is fully encompassed within Nho's disclosure, Nho's method includes the step of dissolving the aPEG in a solvent and then filtering the aPEG solution to substantially reduce contaminant levels prior to combining the aPEG solution with the haemoglobin solution, particularly given the disclosure by Nho that any method known in the art may be used to activate PEG for subsequent conjugation to haemoglobin. Therefore, Davis' method steps of dissolving the aPEG in a solvent and then filtering the aPEG solution to substantially reduce contaminant levels prior to using the filtered aPEG solution in haemoglobin modification are not excluded from Nho's disclosure, but are expressly included. What is characterized by Applicants as the critical element of the claimed invention is thus disclosed by Nho *et al.* Whether or not the chemically modified hemoglobin solution of Nho *et al.* is further filtered and sterilized is irrelevant since the claimed method does not exclude such a step. Note that the claimed method includes the open claim language 'method comprising' steps (a), (b) and (c). Applicants should note that the transitional limitation 'comprising' similar to the limitations, such as, 'having', 'including', 'containing' or 'characterized by' represents open-ended claim language and therefore does not

exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). On the other hand, the limitation 'consisting of' represents closed claim language and excludes any element, step, or ingredient not specified in the claim(s). *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948).

The Office has established a prima facie case of anticipation under 35 U.S.C. § 102. The rejection stands.

8) The rejection of claim 17 made in paragraph 11 of the Office Action mailed 11/16/04 under 35 U.S.C. § 103(a) as being unpatentable over Nho *et al.* (US 5,234,903 - Applicants' IDS) as applied to claim 16 above, is maintained for reasons set forth therein and herebelow.

Applicants submit the same arguments on Nho *et al.* as discussed above. Applicants contend that the plastic housing and the O-ring components of the 0.2 micron Zetapor nylon filter make the filter incompatible with filtration of solvents such as methanol, toluene/dichloromethane etc.

Applicants' arguments have been carefully considered, but are not persuasive. Applicants are referred to the Office's response above on their arguments on Nho's disclosure. No evidence is made of record establishing that a nylon filter such as Zetapor membrane filter is incompatible with filtration of organic solvents. In fact, the art documents that methanol-containing solutions are indeed filtered through Zetapor membranes or equivalents thereof. See for example, section 0036 of Somberg *et al.* (US 20040067898 A1). The rejection stands.

Remarks

9) Claims 12-19 stand rejected.

10) THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the

date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

12) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

13) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2005


S. DEVI, PH.D.
PRIMARY EXAMINER